Investigation of dual layer hollow fiber mixed matrix membranes characteristics for toxin removal from blood

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Resumo

Neste trabalho uma nova membrana com características inovadoras foi estudada para um possível futuro uso em tratamentos de pacientes em estágio final da doença renal. Estas membranas são fibras ocas de dupla camada com partículas de carvão activado incorporadas no interior da membrana da camada exterior.

Algumas simulações foram realizadas em COMSOL para comparar o desempenho das membranas de fibra oca de dupla camada de matriz mista com membranas mais finas e sem adsorventes incorporados. Foi demonstrado que a taxa de remoção nas membranas de matriz mista é dependente no grau de saturação do carvão activado e da sua capacidade de adsorção. De qualquer forma, foi concluído que é possível melhorar a remoção de toxinas devido à reacção de adsorção.

Palavras-chave: membrana de matriz mista, carvão activado, creatinina, adsorção.
Abstract

In this work a new membrane with novel characteristics was studied for a possible future use in the treatment of patients with end-stage renal disease. These particular membranes are dual layer hollow fibers with activated carbon particles incorporated inside the exterior layer membrane.

Some simulations were performed in COMSOL to compare the performance of the dual layer hollow fiber mixed matrix membrane with a thinner membrane without any sorbent. It was demonstrated that the removal rate in the mixed matrix membranes is highly dependent on the saturation level of the activated carbon and on its capacity of adsorption. It was concluded that is possible to improve the removal of uremic toxins with the adsorption reaction.

Keywords: mixed matrix membrane, activated carbon, creatinine, adsorption.
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List of abbreviations

AC – Activated carbon
Albumin₀ – Total albumin concentration in the blood solution
c – Creatinine concentration (mg mL⁻¹)
\( c_{ads} \) – Concentration of adsorbed toxin (mol m⁻³)
\( c_t \) – Concentration of a toxin (mol m⁻³)
CFU – Colony-formation units
crt – Creatinine
\( C_{total} \) – Concentration of the toxin’s free fraction and bound fraction together (mol m⁻³)
D – Diffusion coefficient (m² s⁻¹)
ESRD – End-stage renal disease
EU – Endotoxins units
\( F_B \) – Blood’s flow rate (m³ s⁻¹)
\( F_D \) – Dialysate’s flow rate (m³ s⁻¹)
J – Flux (mol m⁻² s⁻¹)
K – Dissociation constant of the adsorption reaction (mg mL⁻¹)
\( k_a \) – Specific adsorption rate (mL mg⁻¹ s⁻¹)
\( k_d \) – Specific desorption rate (s⁻¹)
\( K_{eq} \) – Equilibrium constant (m³ mol⁻¹)
MW – Molecular weight
r – Distance from the center of the hollow fiber
R₁ – Inner radius of the hollow fiber (m)
R₂ – Inner radius plus the inner layer thickness of the hollow fiber (m)
R₃ – Outer radius of the hollow fiber (m)
R₄ – Inner radius of the tube that contains the hollow fiber (m)
t – Time (s)
TMP – Transmembrane pressure

[tox]_{b_{\text{in}}} – Concentration of toxins at the entrance of the blood domain (mol m\(^{-3}\))

[tox]_{b_{\text{out}}} – Concentration that leaves the blood domain (mol m\(^{-3}\))

v – Velocity of the fluid (m s\(^{-1}\))

V – Volume of the solution (mL)

V_b – Blood’s volume (m\(^3\))

v_{\text{blood}} – Velocity of the blood (m s\(^{-1}\))

v_{\text{dialysate}} – Velocity of the dialysate (m s\(^{-1}\))

v_{\text{max blood}} – Maximum velocity of the blood (m s\(^{-1}\))

v_{\text{max dialysate}} – Maximum velocity of the dialysate (m s\(^{-1}\))

W – Mass of activated carbon (g)
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Figure 1 - Representation of the dual layer hollow fiber mixed matrix membranes for blood purification

Figure 2 - Diagram of the hollow fiber module. The harrows represent the velocity profile of the blood and dialysate and the gray region shows the model domains. R1 is the inner radius, R2 is the inner radius plus the inner layer thickness, R3 is the outer radius and R4 is the inner radius of the tube that contains the hollow fiber.

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1. Introduction

1.1 Kidney failure

The kidneys are two organs with the average size of a fist located in the abdominal cavity. Their main function is to remove excess water and waste products of metabolism, such as nitrogen products like urea, creatinine (crt), among others. Besides that, also maintain the homeostasis of electrolytes removing several salts and regulate the acid-base balance. In addition, human kidneys perform a few endocrine and metabolic functions, such as production of the hormone erythropoietin and conversion of vitamin D to its active form [1].

Kidney failure can be due to a trauma, poisoning or caused by a degenerative process instigated by diabetes, high blood pressure or other diseases [1]. In 2008 there were reported approximately 535000 patients under end-stage renal disease (ESRD) in the USA [2]. In order to survive, these patients need a kidney transplant or periodical treatments to remove the excess of water and uremic toxins in the blood.

1.2 Uremic toxins

After kidney failure there is a progressive retention of molecules in the blood that interact negatively with normal biological functions. These molecules are called uremic toxins and can be classified in three groups based on their physiochemical proprieties that influence their dialytic removal. The classification is made based in the molecular weight (MW) or in the ability to bind to proteins like albumin. Uremic toxins with MW inferior to 500 Da are classified as small water-soluble molecules, while molecules with MW from 500 Da to approximately 15000 Da are called middle molecules. Independently of the MW, if a uremic toxin is capable of binding to a protein it belongs to the category of protein-bound toxins [1] and [3].

1.2.1 Small water-soluble molecules

These are the most common uremic toxins and in higher concentrations [4]. These molecules are removed easily by diffusion [1], since they pass without difficulties the
membrane pores and smaller molecules have higher diffusive coefficients by the Stokes-Einstein equation for the diffusion.

The most known small water-soluble molecules are urea (MW = 60 Da) and creatinine (MW = 113 Da), because they are the most concentrated uremic toxins. These two molecules are usually measured to test the conditions of the kidneys, although their biologic activity is limited [4]. In membranes processes, their clearance may be measured to estimate the performance of that treatment, even though the clearance of urea or creatinine can only correlate with the clearance of other small water-soluble molecules [5].

1.2.2 Middle molecular solutes

This class of toxins is essentially peptides or cytokines [4]. The removal of these molecules is more difficult, since the clearance by diffusion decreases with the increase of the molecular weight. This way, their removal should be enhanced by convection, using high-flux membranes and applying transmembrane pressure. One other possibility is to increase the internal filtration. Internal filtration consists in the total water flux across the membrane, where some water passes from the blood to the dialysate close to the blood inlet and returns to the blood near the blood outlet (back filtration). This can be induced increasing the length or decreasing the diameter of the fibers, or increasing the pressure drop in the dialysate [1]. In this case, it is important to mention that the dialysate should not be the standard-quality dialysis fluid, but an ultrapure dialysis fluid, in order to be safe for the patient in terms of endotoxin contamination risk [6].

1.2.3 Protein-bound uremic toxins

In a review done in 2003 where 90 molecules identified as uremic toxins were classified, 27.8% of all molecules were protein-bound toxins, having most of them a MW inferior to 500 Da [4]. Since then, more protein-bound toxins have been identified as well as their toxic effects. These compounds were documented being involved in the progression of chronic kidney disease and in generation of cardiovascular disease [3] and [7].

Protein-bound toxins associate with blood proteins like albumin, which molecular weight is 66 kDa. Since blood proteins should be retained during any treatment, the removal of protein-bound toxins is very difficult and limited to the free fraction of those toxins [1] and [8].
However, the binding reaction of albumin is reversible, thus existing an equilibrium between the free and bounded toxin concentrations. This way, the removal is inversely related to the affinity constant of these toxins with albumin [7].

Meyer et al. (2004) showed that the clearance of this class of toxins can be improved increasing the dialyzer mass transfer area coefficient, dialysate flow rate or adding a sorbent in the dialysate [9]. Other possibility that should be investigated is to stimulate the dissociation of these toxins with albumin using chronic acidosis or hypoalbuminemia as example [7]. Some diets or the consumption of sorbents orally may also inhibit the intestinal absorption of these toxins or its precursors [7].

1.3 Treatments for end-stage renal disease

There are several treatments for end-stage renal disease which allow extending the life of the patients in some years, being the best one the kidney transplant [2]. However, this option is limited to the number of kidney available and the compatibility with the donor. This way, other treatments have to be done, where the function of the kidneys is mimicked artificially.

1.3.1 Hemodialysis

Hemodialysis is the most common treatment for ESRD, with nearly 1,4 million uretic patients treated worldwide in 2004 [10].

In this treatment the blood is pumped out of the body to the dialyzer, where flows in the lumen of hollow fibers membranes (0,4 - 2,6 m$^2$ surface area), while the dialysate flows in the dialyzer shell counter currently. The hollow fiber membrane acts as a barrier that retains blood proteins and cells, while removing low molecular weight waste metabolites from the blood to the dialysate. The toxins removal is based on their diffusivity in the membrane, which is dependent on their molecular weight. This way, to prevent the depletion of the blood’s electrolytes, the dialysate should contain a similar concentration of electrolytes, which also equalize the transmembrane osmolarity. The blood’s flow rate is limited by the quality of the vascular accesses, but with an average of 400 mL/min. On the other hand, the flow rate of the dialysate should be between 1,5 – 2 times higher than the blood’s flow rate [1] and [10].
Hemodialysis is very effective removing small uremic toxins, but for larger toxins the removal is lower, due to the sieving properties of the membrane [10]. The elimination of protein-bounded toxins is equally low, because only the small fraction of unbound toxins can diffuse through the membrane. For the filtration of the excess water, a transmembrane pressure difference can be applied, controlling easily the amount of water removed [10].

This treatment is normally done three times per week with an average duration of 3.5 h [1] and [10].

### 1.3.2 Hemofiltration

In this technique, blood is removed to a hemofilter, where plasma water and toxins are filtered. Hemofiltration as like other convective treatments was developed with the purpose to remove middle molecular weight toxins. In this treatment molecules up to 15 kDa are eliminated from the blood thought ultrafiltration-membranes by a convection mechanism triggered by an applied transmembrane pressure. These membranes are usually 10 times more permeable to plasma water then the membranes from hemodialysis. However, they should be as well capable of retaining the blood proteins and cells [10].

Since that the main mechanism of removal is convection, the small molecules are just dragged from the water flux, being the concentration at the filtrate similar to the plasma concentration. This implies that the removal of small molecules is not as efficient as in the hemodialysis [10].

Due to the higher plasma water loss, the ultrafiltrate produced has to be replaced completely or partially by a replacement fluid with electrolytes. The replacement fluid can be introduced in the blood upstream (pre-dilution), downstream (post-dilution) or in both at the same time [10] and [11].

### 1.3.3 Hemodiafiltration

Hemodiafiltration is a combination of the treatments hemodialysis and hemofiltration [6]. To improve the poor removal of low molecular weight solutes in hemofiltration, a dialysate fluid is circulated in the shell of a hemofilter counter currently, causing a concentration gradient that provokes the diffusion of small molecular weight molecules out of the blood [1]. On the
other hand, the convective flow imposed in this method results in a better deduction of the excess water and the higher molecular weight molecules [6].

As applied in hemofiltration, a replacement fluid may be needed. This substitution fluid can also be administered either before, after or both before and after the filter. Whenever a substitute fluid is needed, the standard-quality dialysis fluid should be replaced by a ultrapure dialysis fluid characterized by having a bacterial count in colony-formation units (CFU) inferior to 0.1 CFU/mL and an endotoxin count in endotoxins units (EU) inferior to 0.05 EU/mL [6].

A study showed that post-dilution hemodiafiltration removes more β₂-microglobulin, a middle molecule, than the pre-dilution mode [12]. However, in patients with high hematocrit levels or blood protein concentration, pre-dilution proved to be better [6]. Pre-dilution has the disadvantage of diluting the blood toxins, reducing their clearances, but has the advantage of diminish the blood’s viscosity and hemoconcentration, preventing clottings in the membrane [13]. Besides that, dilution might also increase the removal of protein-bound toxins by augmenting the free fraction available for removal [12].

The high-flux membrane used in hemodiafiltration may cause some albumin loss that may result in the clearance of more protein-bound toxins, though it is unclear how beneficial this albumin loss may be [6]. Nevertheless, the removal of protein-bound toxins still poor in this treatment.

The treatments hemodiafiltration and hemofiltration have typically the same duration and frequency as the hemodialysis [1].

**1.3.4 High flux dialysis**

Hemodialysis using high flux membranes allows the removal of a larger range of toxins by convective transport [14] and [15]. These membranes have a larger hydraulic permeability coefficient which results in higher amounts of ultrafiltration produced during the treatment [14] and [15].

Although that in hemodiafiltration the removal of middle molecular weight molecules is higher, high flux dialysis may not need a replacement fluid [15]. This is achieved promoting internal filtration [1], [14] and [15]. Internal filtration consists in the total water flux across the membrane, where some water passes from the blood to the dialysate close to the blood inlet and returns to the blood near the blood outlet (back filtration) [1] and [6]. This can be induced
increasing the length or decreasing the diameter of the fibers, or increasing the pressure drop in the dialysate [1], [14] and [15]. Since that part of the dialysate fluid is back filtrated to the blood, the dialysate should be ultrapure dialysis fluid.

1.3.5 Hemoperfusion

In this treatment the blood is pumped to an adsorption column, where several uremic toxins are adsorbed. The most common adsorbers are resins and activated carbon (AC), due to their adsorptive capacity and ability to remove harmful molecules. However, there are some concerns due to the possible release of particles to the blood, lack of biocompatibility or poor homogeneity. To improve the safety of this treatment, the sorbents should be coated with a biocompatible polymer [16].

Hemoperfusion alone is not a very efficient treatment for uremic patients, because of its limited removal of some toxins like urea and since there is not removal of the excess water these patients accumulate [16]. However, when combined with other treatments like hemodialysis the removal of middle molecules and protein-bound toxins is increased, improving the patient’s conditions and reducing the weekly treatment time [16] and [17]. Unfortunately, hemodialysis-hemoperfusion treatment is more expensive and complex [16].

1.4 Mixed Matrix Membrane

Based on the advantages of the hemodialysis-hemoperfusion treatment, came the idea of using mixed matrix membranes, in an attempt of combining diffusion and adsorption of uremic toxins in only one step [2]. This way the removal of toxins in the hemodialysis treatment could be improved and some limitations in the conventional hemoperfusion like inhomogeneous blood flow distribution, stagnation phenomena within the column or high pressure drop could be overcome [16].

Meyer et all demonstrated in 2007 that having an adsorbent in suspension in the dialysate increases the clearance of protein-bound toxins [9]. This way is expectable that having an adsorbent incorporated in the membrane may have a similar effect, continuing to have a simple treatment.
The hollow fiber mixed matrix membranes should be composed by two layers: a macro-porous membrane layer with adsorptive particles incorporated and an extra particle-free inner membrane layer on the blood-contacting side [2]. In error! A origem da referência não foi encontrada. is illustrated the lateral view of this hollow fiber membranes, showing the two membrane layers.

The particle-free inner membrane layer is very important to prevent particle release into the blood and to improve membrane hemocompatibility, since that the blood should not be in direct contact with the activated carbon [2].

![Diagram of dual layer hollow fiber mixed matrix membranes for blood purification.](image)

**Figure 1** - Representation of the dual layer hollow fiber mixed matrix membranes for blood purification.

2. **Experimental**

2.1 **COMSOL modeling**

A dialysis process was modeled using the software COMSOL. This model was based on a similar one presented as example in the COMSOL website (appendix 1).
For this work a dual layer hollow fiber mixed matrix membrane with the dimensions presented on table 1 and a length of 25 cm was modeled inside a tube with 8 mm diameter.

Table 1 – Average dimensions and activated carbon loading in the dual layer hollow fiber mixed matrix membranes with the respective standard deviation.

<table>
<thead>
<tr>
<th>Outer diameter (μm)</th>
<th>984± 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner diameter (μm)</td>
<td>669± 9</td>
</tr>
<tr>
<td>Inner layer thickness (μm)</td>
<td>49± 5</td>
</tr>
<tr>
<td>Mixed matrix layer thickness (μm)</td>
<td>111± 4</td>
</tr>
</tbody>
</table>

In the lumen of the hollow fiber was simulated the passage of a toxin dissolved in water (blood solution), while outside the hollow fiber circulates only water (dialysate).

In figure 2 is described the different components of the model.
Due to the symmetry in the $r$ axis of the hollow fiber module, it is possible to describe it using a 2D model in COMSOL for only half of the entire module, as it is shown by the light grey region in figure 2. This means that this model is composed by 4 domains: blood, inner membrane, mixed matrix membrane layer and dialysate.

This model should be able to predict the total flux of a toxin inside each domain and this way, predict the removal from the blood solution. In equation 1 is shown the differential equation for the total flux.

$$\nabla j = \nabla (-D \times \nabla c_t + v \times c_t)$$

Equation 1
Here $\nabla$ is the differential operator in the coordinates that define this system, $J$ is the flux $(\text{mol m}^2 \text{s}^{-1})$, $D$ is the diffusion coefficient of the toxin $(\text{m}^2 \text{s}^{-1})$, $c_i$ is the concentration of the toxin $(\text{mol m}^3)$ and $v$ is the velocity of the fluid $(\text{m s}^{-1})$.

The total flux has a convective and a diffusive component. The convective component $(v \times c_i)$ will only take place at the blood’s and dialysate’s domain. On the other hand, the diffusive component $(-D \times \nabla c_i)$ will be calculated in all domains, but with a different value for the diffusion coefficient inside the membranes.

COMSOL solves the differential equations by numeric methods. This means that these equations are solved by iterations doing small increments of time and space and predicting the next values based on the previous ones. In order to do this, a time step has to be defined and also all domains are fragmented in small portions. Then the flux in each fragment is calculated based on the flux in the previous fragments.

Besides the equation for the total flux is also necessary an equation to define the flux in the boundaries between different domains. For this purpose was used an empirical equation (equation 2).

$$J = M \times (c_i - K \times c_j) \quad \text{Equation 2}$$

In which $c_i$ and $c_j$ are the concentrations at different domains $(\text{mol m}^3)$, $K$ is the partition coefficient, which should be only multiplied by the concentration at the blood’s and dialysate’s domain and $M$ is a nonphysical velocity $(\text{m s}^{-1})$ that defines how fast the equilibrium in the boundary is reach.

Equation 2 is only applied for the fragments of the 2 domains in contact with the boundary that separate them. Due to the proximity, the concentrations in those fragments should be in equilibrium very fast. This way the value of $M$ should be high enough to ensure this equilibrium and a continuous flux across the interfaces. The chosen value was $10000 \text{ m s}^{-1}$. The partition coefficient was admitted to be equal to 1, because tests performed with clean water showed that these membranes have high clean-water permeance, which means that creatinine is very small compared with the pore size of these membranes [2].

To avoid an excessive amount of calculations this model was scaled in the z-coordinate. So in order to do that, this coordinate was divided by a scale factor of 250. This affected the length of the membrane module, the velocity of the blood and dialysate and also the diffusion in the z axis.
2.1.1 Blood domain

For the convective component of the total flux is necessary to define an equation for the blood’s velocity inside the hollow fiber. Based on the flow rates used during the experiments and the inner radius of the hollow fiber, it was possible to calculate the Reynod’s number and verify that the blood solution is in laminar flow regime. This way, for a fully developed laminar flow, the equation obtained for the blood’s velocity \( v_{\text{blood}} \) in the \( z \)-coordinate was:

\[
v_{\text{blood}}(r) = v_{\text{max,blood}} \times \left(1 - \left(\frac{r}{R_1}\right)^2\right)
\]

Equation 3

In which \( R_1 \) is the inner radius, \( r \) is the distance from the center of the hollow fiber and \( v_{\text{max,blood}} \) is the maximum velocity of the blood obtained for \( r=0 \). The \( v_{\text{max,blood}} \) parameter was obtained based on the equations 4 and 5.

\[
F_B = \iint r \times v_{\text{blood}}(r) \, dr \, d\theta
\]

Equation 4

In equation 4 \( F_B \) is the blood’s flow rate, which means that knowing this flow rate and solving the double integral it is possible to obtain an expression for the \( v_{\text{max,blood}} \) (Equation 5).

\[
v_{\text{max,blood}} = \frac{2 \times F_B}{\pi \times R_1^2}
\]

Equation 5

Due to the scale done the final expression for the velocity must be divided by the scale factor of 250.

For the diffusion component it was introduced the diffusion coefficient of the toxin presented. However this coefficient cannot be isotropic, because the \( z \) axis was scaled. Since in equation 1 the concentration is differentiated twice in the diffusion term, the diffusion coefficient in the \( z \)-coordinate must be divided by the square of the scale factor.

In all simulations the flow rate of the blood was 6,667E-8 m\(^3\) s\(^{-1}\).

2.1.2 Dialysate domain

In this domain was also necessary to calculate an equation for the dialysate’s velocity between the hollow fiber and the tube. The equation obtained in the \( z \)-coordinate for the stationary state and laminar flow is presented on equation 6.
In this equation $R_3$ is the outer radius, $R_4$ is the radius of the tube that contains the hollow fiber, $r$ is the distance from the center of the hollow fiber and $v_{\text{max,dialysate}}$ is the maximum velocity of the dialysate obtained for $r = \frac{R_3 + R_4}{2}$. The $v_{\text{max,dialysate}}$ is multiplied by a minus signal, because the dialysate flows in the opposite direction of the blood. This parameter was obtained applying equation 15 for the dialysate’s velocity and flow rate and the result is equation 7.

\[
v_{\text{max,dialysate}} = \frac{3 \times F_D \times (R_4 - R_3)^2}{2 \times \pi \times [-6 \times R_3 \times R_4 \times (R_4^2 - R_3^2) - 3 \times (R_4^4 - R_3^4) + 4 \times (R_3 + R_4) \times (R_4^3 - R_3^3)]}
\]

Equation 7

In which $F_D$ is the dialysate’s flow rate ($m^3 \cdot s^{-1}$).

The final expression of the dialysate’s velocity was also divided by the scale factor and the diffusion coefficient was the same as for the blood, being the diffusion coefficient in the $z$-coordinate divided by the square of the scale factor as well.

In all simulations the dialysate’s flow rate was $5,333E-7$ $m^3 \cdot s^{-1}$.

### 2.1.3 Inner membrane layer domain

In this layer there is only diffusion of toxins. This way was defined a diffusion coefficient for the toxin inside the membrane, which was divided by the square of the scale factor for the $z$-coordinate.

### 2.1.4 Mixed matrix membrane layer domain

In this domain there is an adsorption reaction. Equations 8 and 9 were used to calculate the concentration of the free and bound toxin.

\[
\frac{dc}{dt} = -k_a \times c \times (c_{\text{max}} - c_{\text{ads}}) + k_d \times c_{\text{ads}}
\]

Equation 8
\[ \frac{dc_{ads}}{dt} = k_a \times c \times (c_{max} - c_{ads}) - k_d \times c_{ads} \]  

Equation 9

In these equations \( c \) is the concentration of free toxin (mol m\(^{-3}\)), \( k_a \) is the specific adsorption rate (m\(^3\) mol\(^{-1}\) s\(^{-1}\)), \( k_d \) is the specific desorption rate (s\(^{-1}\)), \( c_{max} \) is the maximum adsorption capacity per volume of mixed matrix membrane (mol m\(^{-3}\)) and \( c_{ads} \) is the concentration of adsorbed toxin (mol m\(^{-3}\)).

Only the free toxin can diffuse and its diffusion coefficient was the same as for the inner membrane layer.

2.2 COMSOL simulations

After defining the model and all the relevant parameter, two simulations were performed for each type of uremic toxins. One simulation was done with the four domains previously described, while the other simulation was performed without the mixed matrix membrane domain. Figures 3 and 4 illustrate the difference between the models of the two simulations.

![Figure 3 - Simulation with adsorption of toxins. Domains represented from left to right: Blood, inner membrane, mixed matrix membrane and dialysate.](image)
Both axis display the dimensions of the domains. In the horizontal axis is shown the dimensions from table 1 plus the 4 mm radius of the tube where flows the dialysate and from the vertical axis is possible to verify that the length of the membrane domain is 1 mm. This happens because the average length admitted was 25 cm, but this length was reduced 250 times due to the scale performed.

For both blood and dialysate was simulated a single pass. This means that the concentration of toxins in the inlet of both domains is constant.

To compare the removal obtained in each pair of simulations, it was calculated the clearance of toxins from the blood. Equation 10 demonstrates how the clearance was calculated.

\[
\text{Clearance} = \frac{[\text{tox}]_{\text{in}} - [\text{tox}]_{\text{out}}}{[\text{tox}]_{\text{in}}} \times F_B \quad \text{Equation 10}
\]

In which \([\text{tox}]_{\text{in}}\) is the concentration of toxins at the entrance of the blood domain, \([\text{tox}]_{\text{out}}\) is the concentration that leaves the blood domain and \(F_B\) is the blood’s flow rate.

### 2.2.1 Small water-soluble molecules simulations

The diffusion coefficient inside the membrane and the kinetic parameters of adsorption were calculated for the creatinine in some experiments performed. The value of the diffusion coefficient admitted inside the membrane was 3,14E-10 m² s⁻¹ and the values of \(k_s\), \(k_a\) and \(c_{\text{max}}\)
calculated in these hollow fiber membranes were 9,87E-3 m³ mol⁻¹ s⁻¹, 0 s⁻¹ and 101 mol m⁻³, respectively.

The diffusion coefficient of creatinine in the solutions was 9,8E-10 m² s⁻¹ [19].

The concentration of creatinine admitted for the blood’s inlet was 0,1 mg/mL, which is equivalent to 0,884 mol m⁻³. The concentration at the dialysate’s inlet was equal to 0 mol m⁻³ in all simulations.

2.2.2 Middle molecules simulations

The initial concentrations were the same as for the small water-soluble molecules (0,884 mol m⁻³). However, since these molecules have a higher molecular weight their partition and diffusive coefficient should be smaller. It was not possible to calculate those coefficients for a middle molecule, so it was admitted some values. The partition coefficient used was 0,7 and the diffusion coefficient in the solutions and in the membrane was calculated based on the values for the creatinine, admitting a molecular weight of 1000 Da for the toxin and knowing that the diffusion coefficient is proportional to the inverse of the molecular weight elevated to one third [18]. In equation 11 is shown how the diffusion coefficient was calculated.

\[
\text{Diff. coefficient}_\text{toxin} = \text{Diff. coefficient}_\text{creatinine} \times \left( \frac{\text{MW}_\text{creatinine}}{\text{MW}_\text{toxin}} \right)^{1/3}
\]

Equation 11

Besides the diffusion and partition coefficient, also the maximum capacity of adsorption was decreased to half the maximum capacity of adsorption of the creatinine. The remainder kinetic parameters of the adsorption reaction used were the same as for the creatinine.

2.2.3 Protein-bound toxins simulations

For these two simulations a new reaction was implemented in the blood domain, where the toxin could bind to albumin. That reaction is shown in the next equation.

\[
\text{Free}_{\text{toxin}} + \text{Albumin} \xrightleftharpoons[k_{-1}]{k_1} \text{Bound}_{\text{toxin}}
\]

Equation 12

In the last equation k₁ is the constant rate for the complex formation and k⁻₁ is the constant rate of the dissociation of the complex.
Based on equation 12, it was calculated the differential equations for the variation of the concentration of the free and bound toxin in time.

\[
\frac{d\text{Free}_{\text{toxin}}}{dt} = -k_1 \times \text{Free}_{\text{toxin}} \times (\text{Albumin}_0 - \text{Bound}_{\text{toxin}}) + k_{-1} \times \text{Bound}_{\text{toxin}}
\]

Equation 13

\[
\frac{d\text{Bound}_{\text{toxin}}}{dt} = k_1 \times \text{Free}_{\text{toxin}} \times (\text{Albumin}_0 - \text{Bound}_{\text{toxin}}) - k_{-1} \times \text{Bound}_{\text{toxin}}
\]

Equation 14

In both equations Albumin\(_0\) is the total albumin concentration in the blood solution.

The rate of complex formation divided by the rate of complex dissociation gives the equilibrium constant. To simulate a toxin with a considerable binding affinity it was used an equilibrium constant equal to 1000 m\(^3\) mol\(^{-1}\). The values for \(k_1\) and \(k_{-1}\) were valued based on the equilibrium constant and with the aim of making the reaction represented in equation 12 fast, in order to reach the equilibrium quickly. This way the value for \(k_1\) was 10000 m\(^3\) mol\(^{-1}\) s\(^{-1}\) and the value for \(k_{-1}\) was 10 s\(^{-1}\).

The concentration of the free and bound fraction at the inlet of the blood was calculated admitting that at the entrance of the blood the concentrations are at equilibrium. Equations 15 and 16 are the expressions for those concentrations.

\[
\text{Free}_{\text{toxin}} = \frac{-\text{Albumin}_0 + C_{\text{total}} - \frac{1}{K_{\text{eq}}} \sqrt{\left(\text{Albumin}_0 - C_{\text{total}} + \frac{1}{K_{\text{eq}}}\right)^2 + 4 \times C_{\text{total}}}}{2}
\]

Equation 15

\[
\text{Bound}_{\text{toxin}} = C_{\text{total}} = \frac{-\text{Albumin}_0 + C_{\text{total}} - \frac{1}{K_{\text{eq}}} \sqrt{\left(\text{Albumin}_0 - C_{\text{total}} + \frac{1}{K_{\text{eq}}}\right)^2 + 4 \times C_{\text{total}}}}{2}
\]

Equation 16

In which \(C_{\text{total}}\) is the concentration of the free fraction and the bound fraction together (mol m\(^3\)) and \(K_{\text{eq}}\) is the equilibrium constant (m\(^3\) mol\(^{-1}\)).

The value of \(C_{\text{total}}\) used was 1 mol m\(^3\) and the concentration of Albumin at the inlet of the blood domain was also 1 mol m\(^3\). Based on these values and on the equilibrium constant, the free fraction obtained was almost 3% of the total toxin concentration.

Once that most of the protein-bound toxins have a molecular weight smaller than 500 Da, the values for the diffusion coefficients and for the partition coefficient used for the free fraction were the same as for the creatinine [4]. On the other hand, the value admitted for the
The diffusion coefficient of the bound fraction was calculated with equation 22 based on a molecular weight of 66 kDa, which is the molecular weight of the albumin. The kinetic parameters of the adsorption reaction used were the same as for the creatinine. Besides that, only the free fraction could diffuse through the membrane.

3. Results and discussion

3.1 Small water-soluble molecules simulation

For some toxins the partition coefficient in the membrane may be smaller than one and it is also expectable that the diffusion coefficient decreases inside the membrane. This means that the membrane has an associated resistance to the flux of toxins from the blood to the dialysate and the bigger is the membrane thickness, the bigger will be that resistance. In order for the membrane to adsorb toxins, it is necessary an extra layer with the sorbent mixed within the membrane. This implies that the membrane thickness has to be higher than the thickness of the conventional membranes already used in treatments like hemodialysis.

Some simulations were performed in COMSOL in order to understand the effect of having a membrane with a larger thickness and the capacity of adsorbing toxins. The toxin removal in the studied membranes was compared with the removal in thinner membranes without sorbents (“conventional” membrane).

The results obtained for the creatinine are presented in figures 5 and 6.
Figure 5 - Creatinine clearance values obtained over time for the studied mixed matrix membrane hollow fiber and for a thinner membrane without sorbents ("conventional" membrane).

Since the membrane polarization and fouling were not taken in account in all simulations, the clearance correspondent to the "conventional" membrane is constant during all simulation time. On the other hand, the clearance in the mixed matrix membrane hollow fiber is highly dependent on the saturation level of the activated carbon, varying in time until it gets totally saturated. This also shows that the clearance will be reliant on the adsorption capacity of the activated carbon to the toxins, meaning that if a toxin is not adsorbed then the
clearance will be most likely worse with the mixed matrix membrane during all treatment time.

At the beginning of the simulation there is an improvement in the removal of creatinine in almost 50% for the mixed matrix membrane hollow fiber, but as the saturation level of the activated carbon increases, the clearance decreases, until that it turns worse at almost 70% saturation of the activated carbon. When the activated carbon gets more saturated, the adsorption reaction turns slower and the creatinine has to diffuse more through the membrane to get adsorbed. Because of that, the effect of having a membrane with a higher thickness turns more pronounced and the clearance decreases.

3.2 Middle molecules simulation

The same comparison was done for the middle molecules using reasonable parameters for this class of uremic toxins.

The simulation results are presented in figures 7 and 8.

![Figure 7 - Middle molecule toxin clearance values obtained over time for the studied mixed matrix membrane hollow fiber and for a thinner membrane without sorbents ("conventional" membrane).](image-url)
At the first instants of the simulation there is also an improvement of almost 30% in the clearance of toxins, but at approximately 30% saturation of the activated carbon, nearly after one hour, the clearance in the “conventional” membrane turns better. Since middle molecules are bigger than the small water-soluble molecules their sieving and diffusive coefficients are smaller and besides that, the maximum capacity of adsorption may be smaller too. Due to all that, the enhancement in the removal caused by the adsorption reaction in the mixed matrix membrane is less significant than for the smaller toxins. With this in mind, a good suggestion may be to enhance the removal of middle molecules by convection.

3.3 Protein-bound toxins simulations

Finally the simulations results for the protein-bound toxins are shown in figures 9 and 10.
Due to the initial concentrations of protein-bound toxins, albumin and the binding equilibrium constant assumed, the free fraction in the blood solution is only 3% of the total toxin concentration. This is the reason why the clearance is so low in both simulations.

Comparing this two simulations, the clearance in the membrane with activated carbon starts to be almost 60% higher than the clearance in the “conventional” membrane, but as seen before, as the activated carbon gets more saturated the removal decreases.

At the end of the 6 hours only 20% of the activated carbon is saturated. The amount of protein-bound toxins being removed is low and that is why at the end of the simulation the
quantity of adsorbed toxin that turns the clearance in the mixed matrix membrane hollow fiber worse was not reached.

During the simulation some images were generated to visualize how the free protein-bound toxin concentration varies along the hollow fiber module. Those images are shown in figures 11 and 12.

As a result of the fast adsorption reaction, when the toxins reach the mixed matrix membrane layer they are quickly adsorbed, being the concentration at this domain close to zero while there is plenty adsorption capacity, as is possible to visualize in figure 11. On the
other hand, when the toxins diffuse to the dialysate, they take more time to diffuse away from the membrane.

In figure 12 there is a higher change in the concentration at the dialysate than in the blood. This happens because only the concentration of the free fraction of toxins is shown and some of the free toxins that are removed from the blood are replaced for others that were bounded to albumin.

John Patzer explained that close to the blood outlet/dialysate inlet some free protein-bound toxins are able to cross the membrane. However, this flux elevates the toxin concentration in the dialysate to values close to the concentration of the free fraction in the blood, reducing the driving force for the removal over much of the membrane [8]. This means that only a small fraction of the membrane has a good performance in the conventional membranes. Yet in the mixed matrix membrane hollow fibers, the quick adsorption reaction maximizes the driving force across the entire membrane, while the activated carbon is not saturated.

As was shown in all simulations, if the toxin is adsorbed by the activated carbon is possible to improve its removal. However is important to keep in mind that after the activated carbon gets saturated the removal gets worse. To avoid this, the treatments using mixed matrix membrane hollow fibers should be done with an excess of hollow fibers to make sure that during the treatment time the activated carbon never gets saturated enough to turn the clearance worse.

4. Conclusions

As an attempt to improve the removal of protein-bound toxins, yet keeping a simple process, came the idea of using dual layer hollow fiber mixed matrix membranes combining the removal by diffusion/convection and adsorption in only one step.

A model was created in COMSOL in order to compare the removal of toxins in the mixed matrix membrane hollow fibers with thinner membranes without sorbents. With the simulations performed in COMSOL it was concluded that the clearance is highly depended on the adsorption capacity of the activated carbon and on its saturation level, decreasing as the
activated carbon gets more saturated. If the toxin can be adsorbed, the adsorption reaction can overcomes the extra resistance promoted by the larger thickness of the mixed matrix membrane, but after the activated carbon gets more saturated the clearance gets worse. On the other hand, if a toxin is not adsorbed the removal will be worse with the mixed matrix membrane during all treatment time. The same extra resistance also affects more molecules with higher molecular weight, which means that the mixed matrix membrane may have a better effect for small toxins then for the middle molecules. For the protein-bound toxins, the adsorption reaction increases the efficiency of the membrane, maximizing the driving force for the removal across the entire membrane, improving the removal of these toxins.

In conclusion, the dual layer hollow fiber mixed matrix membrane may be a promising way to improve the removal of uremic toxin.
Bibliografia


Appendix

Separation Through Dialysis

Introduction
Dialysis is a frequently used membrane separation process. An important application is hemodialysis, where membranes are used as artificial kidneys for people suffering from renal failure. Other applications include the recovery of caustic colloidal hemicellulose during viscose manufacturing, and the removal of alcohol from beer (Ref. 1).

In the dialysis process, specific components are preferentially transported through a membrane. The process is diffusion-driven, that is, components diffuse through a membrane due to concentration differences between the dialysate and the permeate sides of the membrane. Separation between solutes is obtained as a result of differences in diffusion rates across the membrane arising from differences in molecular size and solubility.

This example looks at a process aimed at lowering the concentration of a contaminant component in an aqueous product stream. The dialysis equipment is made of a hollow fiber module, where a large number of hollow fibers act as the membrane. It focuses on the transport of the contaminant in the hollow fiber and through its wall.

Figure 1 shows a diagram of the hollow fiber assembly. A large number of hollow fibers are assembled in a module where the dialysate flows on the fibers’ insides while the permeate flows on their outsides in a co-current manner. The contaminant diffuses through the fiber walls to the permeate side due to a concentration gradient, whereas species with a higher molecular weight, those you want kept in the dialysate, are retained due to their low solubility and diffusivity in the membrane.

Figure 1: Diagram of the hollow fiber module.
Model Definition

This example models a piece of hollow fiber through which the dialysate flows with a fully developed laminar parabolic velocity profile. The fiber is surrounded by a permeate, which flows laminarily in the same direction as the dialysate. This example thus models three separate phases: the dialysate, the membrane, and the permeate. The model domain appears in Figure 2. Assume there are no angular gradients, so you can thus use an axisymmetrical approximation.

![Model domain diagram]

Figure 2: Diagram of the dialysis fiber.

The contaminant is transported by diffusion and convection in the two liquid phases, whereas diffusion is the only transport mechanism in the membrane phase. You can formulate the following mass transport equations to describe the system:

\[
\begin{align*}
\nabla \cdot (-DV c_1 + c_1 \mathbf{u}) &= 0 & \text{in } \Omega_{\text{dialysate}} \\
\nabla \cdot (-D_m \nabla c_2) &= 0 & \text{in } \Omega_{\text{membrane}} \\
\nabla \cdot (-DV c_3 + c_3 \mathbf{u}) &= 0 & \text{in } \Omega_{\text{permeate}}
\end{align*}
\]

where \( c_i \) denotes the concentration of the contaminant (mol/m\(^3\)) in the respective phases, \( D \) denotes the diffusion coefficient (m\(^2\)/s) in the liquid phases, and \( D_m \) is the
diffusion coefficient in the membrane, while \( \mathbf{u} \) denotes the velocity (m/s) in the respective liquid phase.

The fiber is 75 times longer than its radial dimension, in this case 0.28 mm in radius and 21 mm in length. To avoid excessive amounts of elements and nodes you must scale the problem. Therefore introduce a new scaled \( z \)-coordinate, \( \hat{z} \), and a corresponding differential for the mass transports:

\[
\hat{z} = \frac{z}{\text{scale}}
\]

\[
d\hat{z} = \text{scale} \cdot d\hat{z}
\]

In the mass-transport equations, \( \epsilon \) is differentiated twice in the diffusion term, which implies that the diffusive flux vector’s \( z \)-component must be multiplied by \((1/\text{scale})^2\). The convective component is only differentiated once, and therefore must be multiplied by \(1/\text{scale}\). You can introduce the scaling of the diffusive part of the flux as an anisotropic diffusion coefficient where the diffusion in the \( z \) direction is scaled by the factor \((1/\text{scale})^2\). This gives the following diffusion-coefficient matrix:

\[
\mathbf{D} = \begin{bmatrix}
D & 0 \\
0 & D/\text{scale}^2
\end{bmatrix}
\]

To obtain the convective part of the flux, assume fully developed laminar flow both inside and outside the hollow fiber. This allows you to introduce the velocity distributions analytically. For the interior, this example uses the following velocity distribution (Ref. 2):

\[
v^\text{dialysate}_z = v^\text{max}_z \left[ 1 - \left( \frac{r}{R_t} \right)^2 \right]
\]

where \( v^\text{dialysate}_z \) is the axial component of the velocity, \( v^\text{max}_z \) is the maximum velocity in the axial direction, \( r \) represents the radial coordinate, and \( R_t \) equals the inner radius of the hollow fiber. The velocity vector must be multiplied by \(1/\text{scale}\) to account for the new scaled \( z \)-coordinate.
Outside the fiber the velocity profile is more complicated. You can draw a hexagonal-shaped unit cell of the fiber assembly (Figure 3):

Figure 3: Hexagonal-shaped unit cell of the fiber assembly.

By approximating the hexagon with a circle, you can assume that the circle indicates the permeate's position of maximum velocity in the axial direction. In order to characterize the flow profile, the model twice integrates a momentum balance over a thin cylindrical shell (Ref. 2) to eventually get the following analytical expression for the permeate velocity distribution:

$$u_{\text{permeate}}^2 = A \left[ r^2 - R_2^2 - 2 \cdot R_3^2 \cdot \ln \left( \frac{r}{R_3} \right) \right]$$

Here $A (1/(m \cdot s))$ is a constant defined by

$$A = \frac{P_0 - P_L}{4\eta L \cdot \text{scale}}$$

In these equations, $R_2$ and $R_3$ are the radial coordinates of the outer fiber wall and the approximated circle, respectively, $\eta$ (Pa·s) is the permeate's dynamic viscosity, and $P_0 - P_L$ (Pa) represents the pressure drop over a length $L$.

The contaminant must dissolve into the membrane phase in order to be transported through it. The interface conditions between the liquid and membrane phases for the concentration are described by the dimensionless partition coefficient, $K$:

$$K = \frac{c_d^d}{c_d^l} = \frac{c_p^d}{c_p^l}$$
Figure 4 shows a schematic concentration profile. Note that there are discontinuities in the concentration profile at the phase boundaries.

![Diagram](image)

Figure 4: Diagram of the concentration profile across the membrane (see Equation 7).

To obtain a well-posed problem, you must define an appropriate set of boundary conditions; for the relevant notation, see Figure 5.

![Diagram](image)

Figure 5: Boundaries and boundary labels for the modeled system.

At the inlet to the model domain, define concentration conditions as:
\[ c_1 = c_0 \quad \text{at } \partial \Omega_{d, \text{in}} \]
\[ c_3 = 0 \quad \text{at } \partial \Omega_{p, \text{in}} \]  

(8)

At the outlet, assume that the convective contribution to the mass transport is much larger than the diffusive contribution:

\[ (-D \nabla c_i + c_i u) \cdot n = c_i u \cdot n \quad \text{at } \partial \Omega_{d, \text{out}} \text{ and } \partial \Omega_{p, \text{out}} \]  

(9)

Here \( n \) is the normal unit vector to the respective boundary. Further, assume that you have no transport over the symmetry boundaries:

\[ (-D_{\text{sym}} \nabla c_i + c_i u) \cdot n = 0 \quad \text{at } \partial \Omega_{d, \text{sym}} \text{ and } \partial \Omega_{p, \text{sym}} \]  

(10)

Also assume symmetry at the horizontal boundaries of the membrane:

\[ (-D_{\text{m}} \nabla c_2) \cdot n = 0 \quad \text{at } \partial \Omega_{\text{m, high}} \text{ and } \partial \Omega_{\text{m, low}} \]  

(11)

You can verify this assumption after solving the model by studying the very small vertical concentration gradient in the membrane.

**MODEL DATA**

The input data used in this model are listed in the following table:

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>VALUE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D )</td>
<td>( 10^{-9} \text{ m}^2/\text{s} )</td>
<td>Diffusion coefficient, liquid phases</td>
</tr>
<tr>
<td>( D_{\text{m}} )</td>
<td>( 10^{-9} \text{ m}^2/\text{s} )</td>
<td>Diffusion coefficient, membrane</td>
</tr>
<tr>
<td>( R_1 )</td>
<td>0.2 mm</td>
<td>Inner radius, hollow fiber</td>
</tr>
<tr>
<td>( R_2 )</td>
<td>0.28 mm</td>
<td>Outer radius, hollow fiber</td>
</tr>
<tr>
<td>( R_3 )</td>
<td>0.7 mm</td>
<td>Approximative radius, unit cell</td>
</tr>
<tr>
<td>( v_{\text{max}} )</td>
<td>1 mm/s</td>
<td>Maximum velocity, dialysate</td>
</tr>
<tr>
<td>( A )</td>
<td>( -2 \cdot 10^{-3} \text{ l/(m-s)} )</td>
<td>Permeate velocity prefactor</td>
</tr>
<tr>
<td>( K )</td>
<td>0.7</td>
<td>Partition coefficient</td>
</tr>
<tr>
<td>( c_0 )</td>
<td>1 M</td>
<td>Inlet concentration, dialysate</td>
</tr>
<tr>
<td>( M )</td>
<td>( 10^4 \text{ m/s} )</td>
<td>Stiff-spring velocity</td>
</tr>
<tr>
<td>scale</td>
<td>7</td>
<td>Axial coordinate scale factor</td>
</tr>
</tbody>
</table>
Results

The surface plot in Figure 6 visualizes the concentration distribution throughout the three model domains: the dialysate region inside the hollow fiber on the left side, the membrane in the middle, and the permeate to the right.

As the plot shows, the concentration inside the hollow fiber decreases markedly over the first 1 mm from the inlet. The figure further shows the developing diffusion layers on both sides of the fiber wall.

![Surface: Concentration (mol/m^3) Arrow: Total flux]

**Figure 6: Concentration in the three domains.**

The figure also shows the concentration jump that arises at the boundary between the dialysate and the membrane. Also, the maximum concentration in the permeate occurs about 0.35 mm downstream from the inlet. If there is a risk of scaling on the fiber's outer surface due to high concentration of filtrated species, it is largest at the location of this maximum.

Note that this example models only a short piece at the hollow fiber's inlet end. Using a larger scale factor you can model the fiber's entire length.
**Modeling in COMSOL Multiphysics**

Because there are discontinuities in the concentration profile at the boundaries between liquid and membrane phases, you must use three separate variables to describe the concentration in the respective phases. To get continuous flux over the phase boundaries, apply a special type of boundary condition using the stiff spring method. Instead of defining Dirichlet concentration conditions according to the partition coefficient $K$, which would destroy the continuity of the flux, you can define continuous flux conditions that, at the same time, force the concentrations to the desired values:

$$
(-D_m \nabla c_1 + c_1 \mathbf{u}) \cdot \mathbf{n} = M(c_2 - Kc_1) \quad \text{at } \partial \Omega^{d/m}
$$

$$
(-D_m \nabla c_2) \cdot \mathbf{n} = M(Kc_1 - c_2) \quad \text{at } \partial \Omega^{m/d}
$$

$$
(-D_m \nabla c_2) \cdot \mathbf{n} = M(Kc_3 - c_2) \quad \text{at } \partial \Omega^{m/p}
$$

$$
(-D \nabla c_3 + c_3 \mathbf{u}) \cdot \mathbf{n} = M(c_2 - Kc_3) \quad \text{at } \partial \Omega^{p/m}
$$

(12)

Here $M$ is a (nonphysical) velocity large enough to let the concentration differences in the brackets approach zero, thereby satisfying Equation 7. These boundary conditions also give a continuous flux across the interfaces provided that $M$ is sufficiently large.

**References**


**Model Library path:** Chemical_Reaction_Engineering_Module/ Separation_Processes/dialysis

**Modeling Instructions**

**MODEL WIZARD**

1. Go to the **Model Wizard** window.
2 Click the 2D axisymmetric button.

3 Click Next.

4 In the Add Physics tree, select Chemical Species Transport>Transport of Diluted Species (cnds).

5 Click Add Selected.

6 In the Concentrations table, enter the following settings:

   c1

7 In the Add Physics tree, select Chemical Species Transport>Transport of Diluted Species (cnds).

8 Click Add Selected.

9 In the Concentrations table, enter the following settings:

   c2

10 In the Add Physics tree, select Chemical Species Transport>Transport of Diluted Species (cnds).

11 Click Add Selected.

12 In the Concentrations table, enter the following settings:

   c3

13 Click Next.

14 In the Studies tree, select Preset Studies for Selected Physics>Stationary.

15 Click Finish.

GLOBAL DEFINITIONS

Parameters

1 In the Model Builder window, right-click Global Definitions and choose Parameters.

2 Go to the Settings window for Parameters.

3 Locate the Parameters section. In the Parameters table, enter the following settings:

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<thead>
<tr>
<th>NAME</th>
<th>EXPRESSION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
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<td>R1</td>
<td>0.2[mm]</td>
<td>Inner radius, hollow fiber</td>
</tr>
<tr>
<td>R2</td>
<td>0.28[mm]</td>
<td>Outer radius, hollow fiber</td>
</tr>
<tr>
<td>R3</td>
<td>0.7[mm]</td>
<td>Approximate radius, unit cell</td>
</tr>
<tr>
<td>NAME</td>
<td>EXPRESSION</td>
<td>DESCRIPTION</td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>H</td>
<td>21[mm]</td>
<td>Fiber length</td>
</tr>
<tr>
<td>scale</td>
<td>7</td>
<td>Axial coordinate scale factor</td>
</tr>
<tr>
<td>h_max</td>
<td>0.1*R1</td>
<td>Maximum mesh element size</td>
</tr>
<tr>
<td>D</td>
<td>1e-9[m²/s]</td>
<td>Diffusion constant, liquid phases</td>
</tr>
<tr>
<td>Dm</td>
<td>1e-9[m²/s]</td>
<td>Diffusion constant, membrane</td>
</tr>
<tr>
<td>M</td>
<td>1e4[m/s]</td>
<td>Stiff-spring velocity</td>
</tr>
<tr>
<td>K</td>
<td>0.7</td>
<td>Partition coefficient</td>
</tr>
<tr>
<td>c0</td>
<td>1[mol/liter]</td>
<td>Inlet concentration, dialysate</td>
</tr>
<tr>
<td>v1_max</td>
<td>1[mm/s]</td>
<td>Maximum velocity, dialysate</td>
</tr>
<tr>
<td>A</td>
<td>-2e3[1/(m*s)]</td>
<td>Permeate velocity prefactor</td>
</tr>
</tbody>
</table>

**GEOMETRY 1**

1. In the Model Builder window, click Model 1>Geometry 1.
2. Go to the Settings window for Geometry.
3. Locate the Geometry Settings section. Find the Units subsection. From the Length unit list, select mm.

**Rectangle 1**

1. Right-click Model 1>Geometry 1 and choose Rectangle.
2. Go to the Settings window for Rectangle.
3. Locate the Size section. In the Width edit field, type R2.
4. In the Height edit field, type H/scale.
5. Click the Build Selected button.
6. Click the Zoom Extents button on the Graphics toolbar.

**Rectangle 2**

1. In the Model Builder window, right-click Geometry 1 and choose Rectangle.
2. Go to the Settings window for Rectangle.
3. Locate the Size section. In the Width edit field, type R3-R1.
4. In the Height edit field, type H/scale.
5. Locate the Position section. In the r edit field, type R1.
6. Click the Build Selected button.
7. Click the Zoom Extents button on the Graphics toolbar.
**Form Union**
In the **Model Builder** window, right-click **Form Union** and choose **Build Selected**.

**DEFINITIONS**

**Selection 1**
1. In the **Model Builder** window, right-click **Model 1**>**Definitions** and choose **Selection**.
2. Right-click **Selection 1** and choose **Rename**.
3. Go to the **Rename Selection** dialog box and type **Dialysate** in the **New name** edit field.
4. Click OK.
5. Select Domain 1 only.

**Selection 2**
1. In the **Model Builder** window, right-click **Definitions** and choose **Selection**.
2. Right-click **Selection 2** and choose **Rename**.
3. Go to the **Rename Selection** dialog box and type **Membrane** in the **New name** edit field.
4. Click OK.
5. Select Domain 2 only.

**Selection 3**
1. In the **Model Builder** window, right-click **Definitions** and choose **Selection**.
2. Right-click **Selection 3** and choose **Rename**.
3. Go to the **Rename Selection** dialog box and type **Permeate** in the **New name** edit field.
4. Click OK.
5. Select Domain 3 only.

**Variables 1**
1. In the **Model Builder** window, right-click **Definitions** and choose **Variables**.
2. Go to the **Settings** window for Variables.
3. Locate the **Geometric Scope** section. From the **Geometric entity level** list, select Domain.
4. From the **Selection list**, select **Dialysate**.
5. Locate the **Variables** section. In the **Variables** table, enter the following settings:

<table>
<thead>
<tr>
<th>NAME</th>
<th>EXPRESSION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>c_all</td>
<td>c1</td>
<td>Concentration</td>
</tr>
</tbody>
</table>
Variables 2
1 In the Model Builder window, right-click Definitions and choose Variables.
2 Go to the Settings window for Variables.
3 Locate the Geometric Scope section. From the Geometric entity level list, select Domain.
4 From the Selection list, select Membrane.
5 Locate the Variables section. In the Variables table, enter the following settings:

<table>
<thead>
<tr>
<th>NAME</th>
<th>EXPRESSION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>c_all</td>
<td>c2</td>
<td>Concentration</td>
</tr>
</tbody>
</table>

Variables 3
1 In the Model Builder window, right-click Definitions and choose Variables.
2 Go to the Settings window for Variables.
3 Locate the Geometric Scope section. From the Geometric entity level list, select Domain.
4 From the Selection list, select Permeate.
5 Locate the Variables section. In the Variables table, enter the following settings:

<table>
<thead>
<tr>
<th>NAME</th>
<th>EXPRESSION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>c_all</td>
<td>c3</td>
<td>Concentration</td>
</tr>
</tbody>
</table>

TRANSPORT OF DILUTED SPECIES
1 In the Model Builder window, click Model > Transport of Diluted Species.
2 Go to the Settings window for Transport of Diluted Species.
3 Locate the Domains section. From the Selection list, select Dialysate.

Convection and Diffusion 1
1 In the Model Builder window, click Convection and Diffusion 1.
2 Go to the Settings window for Convection and Diffusion.
3 Locate the Diffusion section. From the list box below the $D_{c1}$ table, select Diagonal.
4 In the $D_{c1}$ table, enter the following settings:

<table>
<thead>
<tr>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$D$/scale$^{-2}$</td>
</tr>
</tbody>
</table>
Specify the \( \mathbf{u} \) vector as

\[
\begin{array}{c|c}
0 & r \\
\hline
\nu_1 \text{ max} \cdot (1 - (r/R_1)^2) / \text{scale} & z \\
\end{array}
\]

**Initial Values**

1. In the **Model Builder** window, click **Initial Values**.
2. Go to the **Settings** window for Initial Values.
3. Locate the **Initial Values** section. In the \( c_1 \) edit field, type \( c_0 \).

**Symmetry**

1. In the **Model Builder** window, right-click **Transport of Diluted Species** and choose **Symmetry**.
2. In the **Model Builder** window, click **Symmetry 1**.
3. Select Boundary 1 only.

**Concentration**

1. In the **Model Builder** window, right-click **Transport of Diluted Species** and choose **Concentration**.
2. Select Boundary 2 only.
3. Go to the **Settings** window for Concentration.
4. Locate the **Concentration** section. Select the **Species** \( c_1 \) check box.
5. In the \( c_{0,c1} \) edit field, type \( c_0 \).

**Flux**

1. In the **Model Builder** window, right-click **Transport of Diluted Species** and choose **Flux**.
2. Select Boundary 4 only.
3. Go to the **Settings** window for Flux.
4. Locate the **Inward Flux** section. Select the **Species** \( c_1 \) check box.
5. In the \( N_{0,c1} \) edit field, type \( M^* (c_2 - K^* c_1) \).

**Outflow**

1. In the **Model Builder** window, right-click **Transport of Diluted Species** and choose **Outflow**.
2. Select Boundary 3 only.

**TRANSPORT OF DILUTED SPECIES 2**

1. In the **Model Builder** window, click 2.
2 Go to the Settings window for Transport of Diluted Species.
3 Locate the Domains section. From the Selection list, select Membrane.
4 Locate the Transport Mechanisms section. Clear the Convection check box.

**Diffusion**
1 In the Model Builder window, click Diffusion.
2 Go to the Settings window for Diffusion.
3 Locate the Diffusion section. From the list box below the $D_{c2}$ table, select Diagonal.
4 In the $D_{c2}$ table, enter the following settings:

<table>
<thead>
<tr>
<th>$D_m$</th>
<th>$Dm/scale^{-2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$Dm/scale^{-2}$</td>
</tr>
</tbody>
</table>

**Flux 1**
1 In the Model Builder window, right-click Transport of Diluted Species 2 and choose Flux.
2 Select Boundary 4 only.
3 Go to the Settings window for Flux.
4 Locate the Inward Flux section. Select the Species $c2$ check box.
5 In the $N_{0,c2}$ edit field, type $M^* (K^* c1 - c2)$.

**Flux 2**
1 In the Model Builder window, right-click Transport of Diluted Species 2 and choose Flux.
2 Select Boundary 7 only.
3 Go to the Settings window for Flux.
4 Locate the Inward Flux section. Select the Species $c2$ check box.
5 In the $N_{0,c2}$ edit field, type $M^* (K^* c3 - c2)$.

**Transport of Diluted Species 3**
1 In the Model Builder window, click Model 1>Transport of Diluted Species 3.
2 Go to the Settings window for Transport of Diluted Species.
3 Locate the Domains section. From the Selection list, select Permeate.

**Convection and Diffusion 1**
1 In the Model Builder window, click Convection and Diffusion 1.
2 Go to the **Settings** window for Convection and Diffusion.

3 Locate the **Diffusion** section. From the list box below the $D_{c3}$ table, select **Diagonal**.

4 In the $D_{c3}$ table, enter the following settings:

<table>
<thead>
<tr>
<th>D</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$D / \text{scale}^2$</td>
</tr>
</tbody>
</table>

5 Specify the $u$ vector as

<table>
<thead>
<tr>
<th>0</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A(2 - (r^2) - (R2^2) - 2(R3^2) \log(r/R2)) / \text{scale}$</td>
<td>$z$</td>
</tr>
</tbody>
</table>

**Initial Values I**

1 In the **Model Builder** window, click **Initial Values I**.

2 Go to the **Settings** window for Initial Values.

3 Locate the **Initial Values** section. In the $c3$ edit field, type $0.1 * c0$.

**Flux I**

1 In the **Model Builder** window, right-click **Transport of Diluted Species 3** and choose **Flux**.

2 Select Boundary 7 only.

3 Go to the **Settings** window for Flux.

4 Locate the **Inward Flux** section. Select the **Species c3** check box.

5 In the $N_{0,c3}$ edit field, type $M * (c2 * K * c3)$.

**Concentration I**

1 In the **Model Builder** window, right-click **Transport of Diluted Species 3** and choose **Concentration**.

2 Go to the **Settings** window for Concentration.

3 Locate the **Concentration** section. Select the **Species c3** check box.

4 Select Boundary 8 only.

**Outflow I**

1 In the **Model Builder** window, right-click **Transport of Diluted Species 3** and choose **Outflow**.

2 Select Boundary 9 only.
MESH I

Size
1. In the Model Builder window, expand the Model I>Mesh I node, then click Size.
2. Go to the Settings window for Size.
3. Locate the Element Size section. Click the Custom button.
4. Locate the Element Size Parameters section. In the Maximum element size edit field, type \( h_{\text{max}} \).
5. In the Resolution of narrow regions edit field, type 2.

Free Triangular I
1. In the Model Builder window, right-click Mesh I and choose Free Triangular.
2. Right-click Free Triangular I and choose Build All.

STUDY I
In the Model Builder window, right-click Study I and choose Compute.

RESULTS
The following steps reproduce the plot in Figure 6:

2D Plot Group I
1. In the Model Builder window, expand the Results>2D Plot Group I node, then click Surface I.
2. Go to the Settings window for Surface.
3. In the upper-right corner of the Expression section, click Replace Expression.
4. From the menu, choose Definitions>Concentration \((c_{\text{all}})\).
5. Click the Plot button.
6. Click the Zoom Extents button on the Graphics toolbar.
7. In the Model Builder window, right-click 2D Plot Group I and choose Arrow Surface.
8. Go to the Settings window for Arrow Surface.
9. In the upper-right corner of the Expression section, click Replace Expression.
10. From the menu, choose Total flux \((\text{chds3.tfluxr}_c3, ..., \text{chds3.tfluxz}_c3)\).
11. Locate the Coloring and Style section. In the Scale factor edit field, type 0.5.
12. Click the Plot button.